PATENT COOPERATION TREATY

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FINAL CHECK

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
100675-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE2003/000468	20.03.2003	22.03.2002

International Patent Classification (IPC) or national classification and IPC

A61K 9/18,31/195,31/407,47/02,A61P 29/00//A61P 1/04,A61K9/14,31/4439

Applicant

AstraZeneca AB et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))

      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

   ☒ Box No. I Basis of the report
   ☐ Box No. II Priority
   ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   ☐ Box No. IV Lack of unity of invention
   ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   ☐ Box No. VI Certain documents cited
   ☐ Box No. VII Certain defects in the international application
   ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.09.2003	13.05.2003
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Solveig Gustavsson/BS Telephone No. +46 8 782 25 00

Form PCT/IPEA/409 (cover sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2003/000468

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))
☐ publication of the international application (under Rule 12.4)
☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished
pages* _____ as amended (together with any statement) under Article 19
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished
pages* _____ received by this Authority on _____
pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing *(specify)*: _____
☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2003/000468

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 1-3, 41-42

because:

☒ the said international application, or the said claims Nos. 41-42 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-3 are so unclear that no meaningful opinion could be formed *(specify)*:

Present claims 1-3 relate to a large number of possible active agents and carriers which may have very differing characteristics. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to found for only a small portion of such agents and carriers. Due to

.../...

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box III.2

this lack of support and disclosure it was not possible to perform a search over the whole of the claimed scope. The opinion of this Statement is based on the International Search Report and may be considered to be incomplete with respect to the active agents and carriers used. The opinion is focused on the active agents and carriers mentioned in claims 4 and 19-25.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SE2003/000468

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-40	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-40	NO
Industrial applicability (IA)	Claims	1-40	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents:

D1: Yuasa, Hiroshi et al; "Application of Calcium Silicate for Medicinal Preparation. I. Solid Preparation Adsorbing an Oily Medicine to Calcium Silicate"; Chem. Pharm. Bull. 42(11) 2327-2331
D2: Yuasa, Hiroshi et al; "Studies on the Development of Intragastric Floating and Sustained Release Preparation. I. Application of Calcium Silicate as a Floating Carrier"; Chem. Pharm. Bull. 44(7)1361-1366
D3: WO 0166088 A1
D4: JP 8301763 A (Abstract and translation)

The problem which the present invention aims to solve is to provide a solid drug delivery composition for NO-donating Non Steroidal Antiinflammatory Compounds (NO-donating NSAIDs). The NO-donating NSAIDs often have poor aqueous solublility and are in the form of an oily compound which make them difficult to formulate in conventional solid drug delivery compositions such as tablets. This problem has according to the application been overcome by absorbing the NO-donating NSAID(s) into porous particles.

Document D1 discusses solid preparations made from oily, slightly water soluble drugs (tocopheryl nicotinate is used as example) adsorbed to porous calcium silicate powder, Florite. The article also compares the properties of calcium silicate with those of other commonly used excipients such as dibasic calcium phosphate, crystalline cellulose and cornstarch.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

D2 also relates to preparations using porous calcium silicate particles. It is mentioned that calcium silicate can be widely applied as an absorber of oily drugs and diclofenac sodium is used as a model drug.

D3 discloses self emulsifying drug delivery systems comprising NO-donating NSAIDs and at least one surfactant. The compositions may further comprise an acid susceptible proton pump inhibitor.

In D4 compositions comprising a powdery inorganic carrier, such as magnesium metasilicate aluminate or calcium silicate, a sparingly water soluble medicinal substance and a non-ionic surfactant are described.

D1 is considered to represent the closest prior art. The difference between the compositions of the present invention and those of D1 is that the compositions of the invention comprise NO-donating NSAID(s) as active ingredient and D1 relates primarily to tocopheryl nicotinate. The present application talks of "absorbing" the drug into the porous particles while D1 talks of "adsorbing" the drug to calcium silicate. It is however considered that these two expressions in this case is equivalent while in both cases the idea seems to be that the drug penetrates into the pores of the particles. The application provides no indication that there is any difference in technical effect between the compositions of the invention and the compositions of D1 except from the obvious difference in biological effect of the drugs. The present invention consists in applying the principle of absorbing an oily poorly water soluble drug to porous particles in order to provide a solid composition, to another type of oily, poorly water soluble drugs.

To use a solid drug delivery system, which is known to be useful for an oily, poorly water soluble drug, for preparing a solid drug delivery composition comprising another oily, poorly water soluble drug such as a NO-donating NSAID is considered to be obvious to a person skilled in the art. No unexpected technical effect related to the compositions of the invention compared to the composition known from the prior art of D1 has been presented. The invention according to claims 1-2 is therefore considered to lack inventive step.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

The invention according to claim 3 further differs from D1 in that it comprises NO-donating NSAID(s) in melted form and not a tocopheryl nicotinate in oily form. It is however considered to be obvious to a person skilled in the art that also a melted drug can be absorbed to porous particles and that the difference between oily form and melted form is only a matter of melting point and temperature. Claim 3 is also considered to lack inventive step.

According to claim 4 the porous particles are selected from dibasic calcium phosphate, anhydrous microcrystalline cellulose and pregelatinised starch while the compositions of D1 use calcium silicate (Florite). Calcium silicate is suggested in the description as a possible substance for use as porous particles but it is not comprised by the claim. As the application relates to porous particles in general and does not indicate that any special kind of porous particles show an unexpected technical effect it is considered to be obvious to a person skilled in the art to chose any kind of porous particles known in the art for example those named in claim 4. Further, the Florite particles are in D1 compared to several other excipients for example dibasic calcium phosphate, crystalline cellulose and cornstarch. Although these are shown to have inferior liquid holding ability than Florite (the oily material dibutyl phthalate is used in the tests) it is considered obvious to a person skilled in the art that these materials or very similar materials may be used as absorbents for oily drugs in pharmaceutical compositions. The invention according to claim 4 is not considered to be inventive.

The diameter of the calcium silicate powder particles in D1 is 125 µm, and these are granulated to particles with a diameter of 212-300 (page 2328, column 1, lines 22-23). This falls within the range of claims 5-6. The size of the particles and the pores are not considered to contribute to the inventive step. The use of NO-donating NSAID(s) together with surfactant(s) is known from D3 and D4 discloses compositions comprising a drug and surfactants absorbed to magnesium metasilicate aluminate or calcimum silicate. The NO-donating NSAID(s) specified in the claims are

.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

all known from for example D3 which also discloses the combination of NO-donating NSAID(s) and proton pump (H+, K+-ATPase) inhibitors. The compositions according to claims 5-27 and 36-38 are therefore considered to be obvious variations of the invention and are not considered to involve an inventive step.

The processes according to claims 28-35 are very general and only consist of standard procedures well known to a person skilled in the art. The compositions according to D1, D2 and D4 are prepared in more or less the same way and no unexpected effect of the processes has been shown. The invention according to claims 28-35 is therefore considered to lack inventive step. NO-donating NSAID(s) are known to be used in the treatment of pain and inflammation and the invention according to claims 39-40 is not considered to be inventive.

The inventive step of the invention may be questioned also in relation to D2.